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Chronic Multifocal Chest and Leg pain in a 34-year-old Woman

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History and Physical Examination

A 34-year-old woman presented to our orthopaedic clinic complaining of multifocal pain in her chest and legs. Her initial symptoms began approximately 2 years earlier as mild aches occurring at several places in her legs. The pain was intermittent, was aggravated by weightbearing, and initially was alleviated by antiinflammatory medications recommended by her primary care physician. After several months of waxing and waning symptoms, she began to experience similar pain in her ribs bilaterally, unrelated to deep breathing or exertion but reproducible with deep palpation. She was managed nonoperatively for more than a year by her primary care physician but eventually she had constant, worsening right hip pain develop, which limited her mobility and was not controlled by over-the-counter medications. During this time, she also noted an exacerbation of her baseline leg and rib pain. She was referred to orthopaedic clinic and was seen approximately 1 month after the hip pain developed. She denied fever, chills, weight loss, fatigue, weakness, numbness, or other constitutional symptoms.

Her medical history was remarkable only for severe reflux disease, for which she had been treated unsuccessfully with proton-pump inhibitors and histamine blockers. For control of reflux symptoms, she had been taking several doses of Extra-Strength Maalox® (magnesium hydroxide/aluminum hydroxide; 1000 mg/pill; Novartis Consumer Health, Inc, Freemont, MI) daily for 3 years. Her family history was remarkable for rheumatoid arthritis. She denied current or prior alcohol, tobacco, or drug use.

Physical examination revealed a young woman who was in no apparent distress, was afebrile, and had vital signs within the range of normal for her age group. She had no palpable cervical or supraclavicular adenopathy. Her cardiovascular, pulmonary, and abdominal examinations were unremarkable. She had tenderness to palpation to several of her ribs posteriorly, left ankle at the lateral malleolus, and right hip at the greater trochanter. The hip also was painful during flexion, abduction, and external rotation. Her right side displayed 3/5 iliopsoas and 4/5 quadriceps strength. Otherwise, her extremity examination revealed 5/5 strength in all other muscle groups and no deficits in sensation or limitations of range of motion. She had a severely antalgic gait and guarded her right hip.

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Each author confirms that his or her institution has approved the reporting of this case report, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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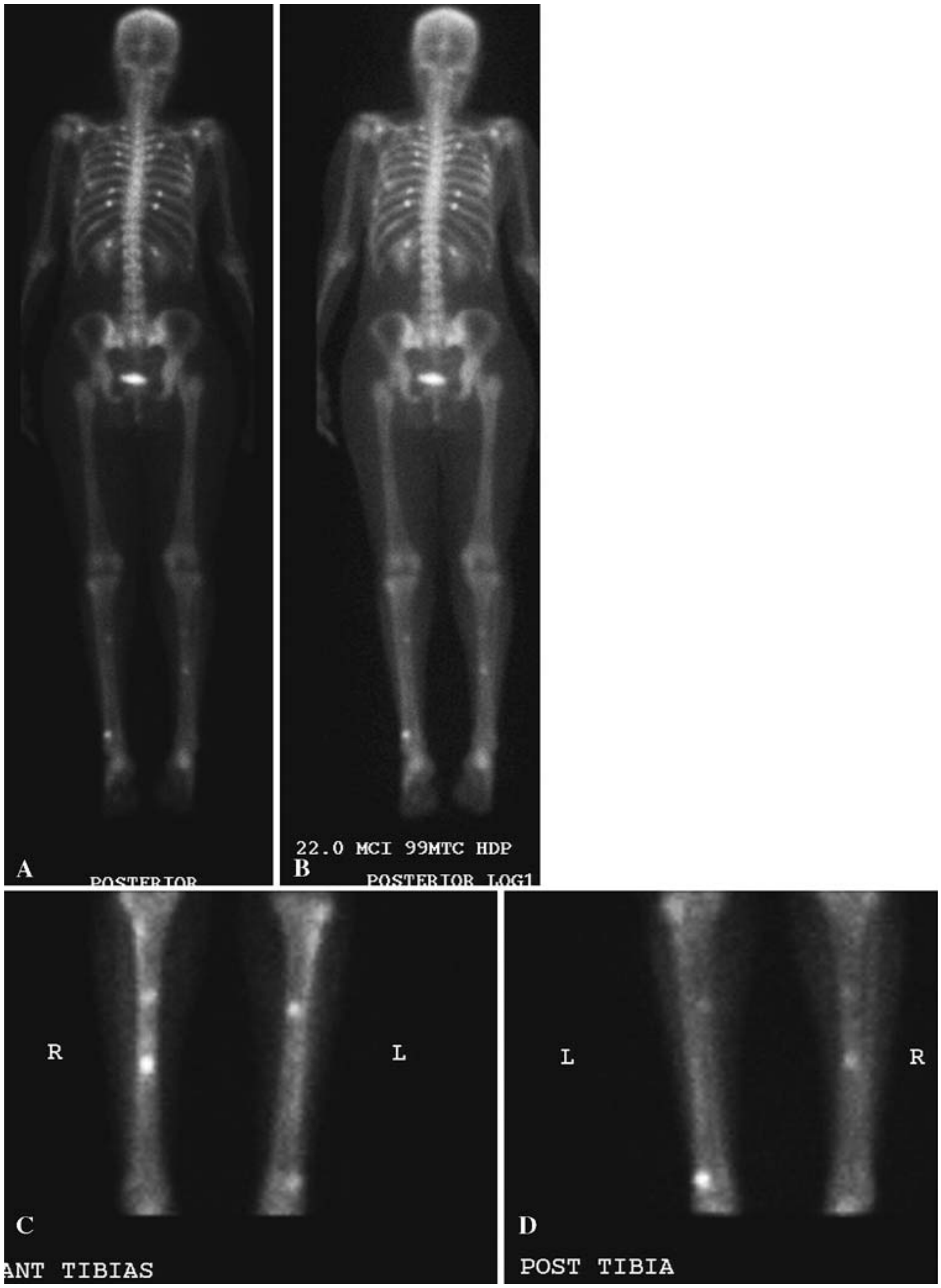

Fig. 1A–D Posterior views of a whole body bone scan with (**A**) darker intensity bone window and (**B**) lighter intensity window show generalized increased uptake. Numerous foci of uptake are seen bilaterally in the ribs, shoulders and lower extremities. No increased uptake is seen in the thyroid or parathyroid region. (**C**) Anterior and (**D**) posterior views of the lower extremities show multiple areas of uptake in the tibias bilaterally with the highest intensity in the right midshaft and left distal tibia.

Laboratory studies showed no abnormalities in basic metabolic panel, including blood urea nitrogen (17 mg/dL [normal, 8–25 mg/dL]), creatinine (0.8 mg/dL [normal, 0.6–1.5 mg/dL]), and calcium (9.8 mg/dL [normal, 8.5–10.5 mg/dL]). Liver and thyroid function panels also were within normal limits. Her automated blood count revealed a leukocyte count of 6200 per cc and low hemoglobin (11.6 g/dL [normal, 12.0–16.0 g/dL]). Further evaluation revealed a normal erythrocyte sedimentation rate (14 mm/hour [normal, 1–25 mm/hour]), normal C-reactive protein (0.9 mg/L [normal, $<$ 8.0 mg/L]), elevated alkaline phosphatase (244 U/L [normal, 30–100 U/L]), and decreased phosphorus (1.9 mg/dL [normal, 2.6–4.5 mg/dL]).

A bone scan was obtained (Fig. 1) along with plain radiographs of the right lower leg and left ankle (Fig. 2). Chest films (Fig. 3) and MRI of the right hip (Fig. 4) also were obtained.

Based on the history, physical examination, and imaging studies, what is the differential diagnosis?

Fig. 2A–B (**A**) In an anteroposterior view of the right leg, the arrow and inset highlight the unilaminar, benign-appearing periosteal reaction in the proximal fibula and osteopenia. (**B**) In a mortise view of the left ankle, the arrow highlights a transverse, linear density in the fibula with cortical irregularity and overall osteopenia.

Imaging Interpretation

A bone scan (Fig. 1) showed a generalized diffuse uptake of radiotracer. Mildly increased uptake was seen in the right hip. Foci of increased uptake were seen in the tibias bilaterally, left distal fibula, and bilaterally in the upper and lower ribs. No increased uptake was seen in the thyroid or parathyroid region. Radiographs showed mild diffuse osteopenia and an area of smooth, unilaminar benign-appearing periosteal reaction along the lateral margin of the right proximal fibular diaphysis (Fig. 2A). A healing, nondisplaced, transverse fracture of the distal fibular diaphysis also was evident (Fig. 2B). A chest radiograph was reported to show multiple rib fractures correlating with findings on bone scan, including the left fourth rib (Fig. 3). MR images showed an area of marrow edema along the compression side of the femoral neck with a central area of linear low signal suggestive of a nondisplaced fracture (Fig. 4).

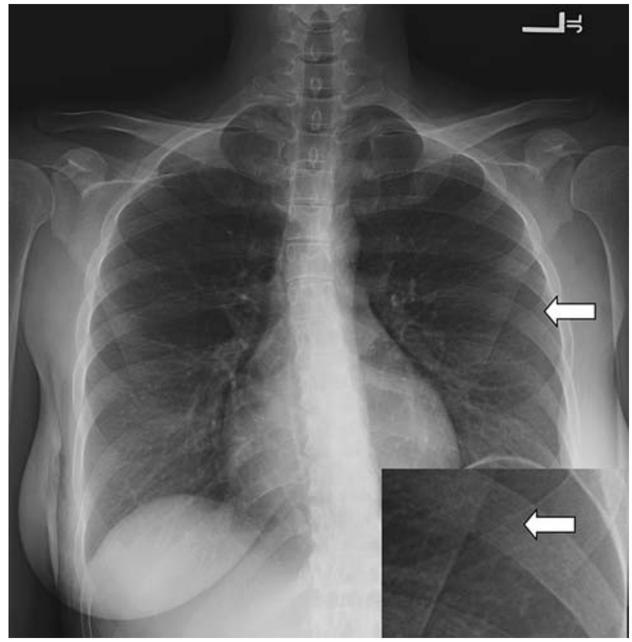

Fig. 3 A chest radiograph shows osteopenia throughout. The inset and arrow note a minimally displaced cortical disruption of the left fourth rib.

Differential Diagnosis

Vitamin D deficiency
Hyperparathyroidism
Metastatic disease
Aluminum toxicity
Hypophosphatemia
Antacid-induced hypophosphatemic osteomalacia

A bone biopsy was not deemed necessary for the diagnosis of this patient. Based on the history, physical examination, imaging studies, and anticipated histology, what is the diagnosis and how should this patient be treated?

Diagnosis

Antacid-induced hypophosphatemic osteomalacia

Fig. 4A–B (**A**) A T2-weighted coronal MR image of the pelvis shows no increased signal in the left hip but an area of increased signal in the base of the right femoral neck. (**B**) An enlarged T2-weighted MR image of the left hip shows a linear low-signal fracture extending to the cortical margin along the compression side of the femoral neck with surrounding T2 hyperintense edema.

Discussion and Treatment

The presentation of a young woman with chronic, multifocal bone pain is concerning for infectious, traumatic, rheumatologic, metabolic, and neoplastic etiologies. This patient had pain for more than 2 years, a normal leukocyte count, and no other constitutional symptoms, making infection less likely. The patient denied any prior trauma. Rheumatologic causes also were unlikely, considering the presenting fracture pattern and negative laboratory workup. Radiographic studies revealed diffuse osteomalacia most consistent with a metabolic etiology. Osteomalacia is characterized by reduced bone density attributable to decreased mineralization of newly formed bone matrix. Underlying abnormalities include abnormal matrix, as in chronic renal failure, and abnormal alkaline phosphatase function, as in hypophosphatasia. Changes in pH at the site of bone formation, as in renal tubular acidosis, also can cause osteomalacia, as can inhibitors of bone formation, such as bisphosphonates.

Mineral deficiencies, such as vitamin D deficiency and hypophosphatemia, also are related to decreased bone mineralization. This disease usually presents as proximal weakness associated with muscle wasting and hypotonia in the lower spine, pelvis, and lower extremities and at sites of pathologic fractures [22]. Osteomalacia usually is indicated radiographically, with nonspecific findings, such as thinning of the cortex and reduced bone density. More specific signs include loss of secondary trabeculae and concavity of the vertebral bodies. Looser zones may be present in the femur and pelvic rami, appearing as narrow (< 5 mm) radiolucent lines lying perpendicular to the cortical margin [9]. Laboratory analysis can show elevated alkaline phosphatase (94%), increased parathyroid hormone (41%), and low calcium or phosphate (47%) [3]. A definitive diagnosis is made with bone biopsy, showing unmineralized matrix, a widened osteoid seam, and high osteoid volume (> 10%). Double tetracycline labeling usually reveals a reduced distance between bands, attributable to decreased skeletal growth rate [22]. In our patient, there was clear clinical and radiographic evidence of osteomalacia. The underlying cause was unlikely to have been an undiagnosed congenital abnormality in mineralization, and considering the patient's normal renal function, mineral deficiency and direct bone inhibition seemed most likely. Although a biopsy-proven diagnosis was not obtained, several clinical characteristics helped rule out certain disorders.

Vitamin D deficiency occurs with decreased sun exposure, decreased intake, malabsorption, defective endogenous processing, and end organ resistance. Laboratory evaluation can reveal secondary hyperparathyroidism, low to low-normal calcium, hypophosphatemia, and elevated alkaline phosphatase. Our patient had a regular diet, normal renal function, and adequate sun exposure, making severe vitamin D deficiency less likely.

Hyperparathyroidism occurs in the setting of adenoma, hyperplasia, and carcinoma, causing increased bone resorption and hypercalcemia in 90% of patients, hypophosphatemia, increased alkaline phosphatase activity, and in some patients, mild metabolic acidosis and normochromic, normocytic anemia [17, 21]. Although 80% of patients are asymptomatic, some may experience fatigue, nephrolithiasis, bone pain, abdominal pain, or psychiatric complaints [23]. Hyperparathyroidism was an unlikely contributor in our patient, who was symptomatic, had a normal serum calcium level and a benign-appearing parathyroid gland on bone scan.

Neoplastic disease, either metastasis or primary hematologic tumor, can present with severe pain, hypercalcemia, pathologic fractures, spinal cord compression, and other nerve compression syndromes [20]. Our patient, however, had a chronic course inconsistent with widespread neoplasm, no radiographic evidence of a distinct primary or metastatic lesion, no constitutional symptoms, and no laboratory evidence of primary or hematologic malignancy.

Aluminum toxicity is a rare disorder that typically occurs in patients receiving total parenteral nutrition [14] and in a small percentage of dialysis patients using aluminum-containing phosphate binders, antacids, and dialysates [13]. Accumulation of aluminum leads to bone pain, weakness, mutism, dysphonia, microcytic anemia, and hypercalcemia. Toxicity can progress to pathologic fractures, seizures, dementia, and death [16]. Radiographic manifestations of aluminum toxicity include demineralization, multiple fractures, avascular necrosis, and destructive arthritis [16]. Although this presentation is similar to that of our patient, there has been only one report of antacid-induced aluminum toxicity in a patient with normal renal function [26].

Hypophosphatemia can occur with increased urinary phosphate excretion, as in hyperparathyroidism and vitamin D deficiency, or with redistribution of phosphate into cells, as in insulin infusion and refeeding syndrome [19]. The most common cause is decreased intestinal absorption, as in dietary deficiency, antacid abuse, and malabsorption. Symptoms include proximal muscle weakness, dysphagia, ileus, bleeding, respiratory depression, congestive heart failure, confusion, seizures, and delirium [15]. The diagnosis is confirmed by simple laboratory testing, and an elevated urinary phosphate secretion (> 100 mg/day) can indicate primarily renal etiologies.

Aluminum-containing antacids are considered first-line therapy for reflux disease [18]. Although generally benign, aluminum- and magnesium-containing antacids can negatively influence bone physiology. Reported cases of antacid-induced osteomalacia typically involve patients who are self-prescribing antacid doses greater than 10 g per day [1, 4, 5, 7, 8, 10, 12, 24]. Chines and Pacifici [5] reviewed 13 such cases and found patients took between 2.3 to 20 g daily for 1.5 to 12 years before diagnosis. The aluminum or magnesium component of these drugs binds dietary phosphate, preventing its intestinal absorption and causing a negative phosphate balance typically within 3 to 4 weeks. The resulting hypophosphatemia is thought to prevent proper nucleation of mineral salts into the bone matrix, causing osteomalacia [6, 11]. In addition, hypercalciuria can appear within 2 weeks [25] and, if not adequately supplemented in the diet, can lead to increased bone resorption via parathyroid hormone [2].

These derangements manifest themselves as skeletal pain and weakness in nearly all cases reported. In one report of patients with antacid-induced hypophosphatemia (0.19–0.77 mmol/L [normal, 0.80–1.60 mmol/L)], eight of 10 had hypercalciuria (4.09–22.60 mmol/day [normal, 1.2–6.2 mmol/day]), nine of nine had hypophosphaturia (0.0–0.96 mmol/day [normal, 9.6–32.3 mmol/day]), 10 of 12 had elevated alkaline phosphatase, and 12 of 12 had normal serum calcium. Radiographic manifestations included diffuse osteopenia in 10 of 13 patients reviewed. Approximately half the patients also had fractures, with pseudofractures and subperiosteal erosions occasionally seen. Fractures typically occurred in ribs 2, 3, and 4, vertebrae, hips, and pelvis [5].

Given the presentation and medication history, a presumptive diagnosis of antacid-induced hypophosphatemic osteomalacia was made in our patient. A bone biopsy was not deemed necessary and, as such, a definitive diagnosis was never made. Histologic reports of patients with similar primary disease, however, consistently show unmineralized matrix seen as widened osteoid seams (> 15 μm), with an osteoid volume greater than 10% [22]. The patient was instructed to discontinue all antacids immediately. Her ankle fracture was treated with a walking boot. Her hip fracture was treated nonoperatively with crutches and instructions to protect weightbearing. For her reflux disease, she was educated on lifestyle modifications and instructed to followup with her primary care doctor immediately for treatment. She had experienced resolution of bone pain and was able to tolerate full weightbearing and resume baseline activity within 3 months of treatment and cessation of antacids. At last followup at 12 months, the patient was free of pain and stabilized on calcium, phosphate, and vitamin D supplementation.

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